

Why we should not recommend or offer fluvoxamine to COVID-19 patients?

Trkulja, Vladimir

Source / Izvornik: **European Journal of Clinical Pharmacology, 2023, 79, 321 - 322**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1007/s00228-022-03447-3>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:779915>

Rights / Prava: [In copyright](#) / [Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2025-01-29**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine
Digital Repository](#)





Why we should not recommend or offer fluvoxamine to COVID-19 patients?

Vladimir Trkulja¹

Received: 29 October 2022 / Accepted: 18 December 2022 / Published online: 23 December 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

To the Editor,

The answer to the posted question is rather straightforward: not only there is no explicit evidence of a benefit of fluvoxamine in COVID-19 patients, but there is rather explicit evidence of no (relevant) benefit. The apparently reasonable pharmacodynamic/pharmacokinetic rationale [1, 2] and a huge amount of observational data (too extensive to be individually addressed here)—although commonly contradictory—have indicated a possibility that early commenced fluvoxamine in COVID-19 outpatients might prevent disease progression; or that fluvoxamine in hospitalized and even critical (e.g., managed in intensive care units, ICU) COVID-19 patients might reduce mortality. Regarding the former (mildly symptomatic COVID-19 outpatients, fluvoxamine within 7 days since diagnosis), randomized placebo-controlled trials (RCT) are rather consistent in showing no relevant benefit: (i) initially, a small STOP-COVID 1 RCT [3] (fluvoxamine 2×100 to 3×100 mg/day, 15 days $n=80$, placebo $n=72$) indicated a reduced 15-day hospitalization/new onset hypoxemia rate, but only 6 events were recorded (0/80 vs. 6/72); (ii) the trial extension, STOP-COVID 2 (never published) [4], however, found no benefit: 11/272 (4.0%) events vs. 12/275 (4.4%); (iii) the TOGETHER trial [5] (fluvoxamine 2×100 mg/day, 10 days, $n=741$, placebo $n=756$) indicated a mild reduction in 28-day hospitalization rates (10.0% vs. 13.0%); (iv) a small South Korean trial (fluvoxamine 2×100 mg/day, 10 days, $n=26$, placebo $n=26$; outcomes as in STOP-COVID) found no indication of a treatment benefit (2 events vs. 2 events) [6]; (v) the recent COVID-OUT RCT [7] (fluvoxamine 2×50 mg/day, 14 days, $n=334$, placebo $n=327$) found similar 14-day rates of a composite of new onset hypoxemia, hospitalization, emergency room visit or death (24.0% vs. 24.9%) and of

each of its components; (vi) finally, the recent ACTIV-6 trial [8] (fluvoxamine 2×50 mg/day, 10 days, $n=674$, placebo $n=614$) reported similar 28-day hospitalization/emergency room visit rates (3.9% fluvoxamine vs. 3.8% placebo) and similar time to recovery (HR=0.96, 95%CrI 0.86–1.07). Recommending or offering a non-functional treatment is unethical, and “publicizing” its existence might generate a false sense of security in those reluctant to receive vaccination if being viewed as a helpful alternative resource.

Why, then, do many colleagues support (in this or that way) the use of fluvoxamine in this setting? To this question, the answer is a more complex one. Undoubtedly driven by good intentions and facing an unprecedented pandemic of a devastating disease, we might have developed a cognitive bias and are prone to see what we would like to see, rather than the objective “state of the matter,” particularly when resources are limited. However, a large part of the problem is elsewhere [9, 10]: (i) much of the published medical research is methodologically inadequate and misleading; (ii) much of

it is both carried out and published for wrong reasons (the latter might be particularly applicable to COVID-19-related manuscripts [11]); (iii) most healthcare professionals are not aware of this problem and lack the skills needed to evaluate reliability and usefulness of data. This is particularly so with non-randomized/observational data which tend to be perceived and interpreted as if coming from valid experiments although commonly burdened by a range of biases unrecognized by the readers, and seemingly also by journal editors (see, e.g., [12] as a worked-out critique of a published study advocating fluvoxamine benefits, which was so heavily flawed that it should best be completely ignored; see [13] for the elaboration of biases particularly common in observational studies on COVID-19).

If the tendency of publishing research on fluvoxamine in COVID-19 that is of highly questionable validity continues, we might find ourselves in a situation that is almost impossible to rectify—we would not be able to discourage the public in their views of fluvoxamine as a “wonder drug,” just as we are unable to rectify the confusion about ivermectin.]

✉ Vladimir Trkulja
vladimir.trkulja@mef.hr

¹ Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, 10000 Zagreb, Croatia

Author contributions This is a Letter to Editor authored by Vladimir Trkulja

Data availability This Letter to Editor contains no data.

Declarations

Competing interests The author declares no competing interests.

References

- Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV (2021) Fluvoxamine: a review of its mechanism of action and its role in COVID-19. *Frontiers Pharmacol* 12:652688. <https://doi.org/10.3389/fphar.2021.652688>
- Dodds MG, Doyle EB, Reiersen AM, Brown F, Rayner CR (2022) Fluvoxamine for the treatment of COVID-19. *Lancet Glob Health* 10(3):e332. [https://doi.org/10.1016/S2214-109X\(22\)00006-7](https://doi.org/10.1016/S2214-109X(22)00006-7)
- Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE et al (2020) Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. *JAMA* 324:2292–2300
- Lenze E. Fluvoxamine for early treatment of COVID-19: a fully-remote, randomized placebo controlled trial. <https://clinicaltrials.gov/ct2/show/NCT04668950>. Accessed 26 Oct 2022
- Reis G, dos Santos Moreira-Silva EA, Medeiros Silva DC, Thabane L, Cruz Milagres A, Santiago Ferreira T et al (2022) Effect of early treatment with fluvoxamine on risk of emergency care and hospitalizations among patients with COVID-19: the TOGETHER randomized platform trial. *Lancet Glob Health* 10:e42-51. [https://doi.org/10.1016/S2214-109X\(21\)00448-4](https://doi.org/10.1016/S2214-109X(21)00448-4)
- Seo H, Kim H, Bae S, Park S, Chung H, Sung H, Jung J et al (2022) Fluvoxamine treatment of patients with symptomatic COVID-19 in a community treatment center: a preliminary result of randomized controlled trial. *Infect Chemother* 54:102–113
- Bramante CT, Juling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM et al (2022) Randomized trial of metformin, ivermectin and fluvoxamine for COVID-19. *N Engl J Med* 387:599–610
- McCarthy MW, Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Felker GM et al (2022) Fluvoxamine for outpatient treatment of COVID-19: a decentralized, placebo-controlled, randomized platform clinical trial. *medRxiv*. <https://doi.org/10.1101/2022.10.17.22281178>
- Ioannidis JPA, Stuart ME, Brownlee S, Strite S (2017) How to survive the medical misinformation mess. *Eur J Clin Invest* 47:795–802
- Altman DG (1994) The scandal of poor medical research. *BMJ* 29:283–284
- Kodvanj I, Homolak J, Virag D, Trkulja V (2022) Publishing of COVID-19 preprints in peer-reviewed journals, preprinting trends, public discussion and quality issues. *Scientometrics* 127:1339–1352
- Trkulja V (2022) Fluvoxamine for COVID-19 ICU patients? *Br J Clin Pharmacol* 88:2454–2455
- Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L et al (2020) Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 11:5749. <https://doi.org/10.1038/s41467-020-19478-2>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.